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PATENT  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : WATSON et al. Confirmation No: 8178  
Appl. No. : 09/975,317  
Filed : October 12, 2001  
Title : METHOD  
TC/A.U. : 1616  
Examiner : M. HARTLEY  
  
Docket No.: : WATS3001C/JDB  
Customer No: : 23364

**SECOND SUPPLEMENTAL RESPONSE**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This response is supplemental to the amendments dated March 17, 2004 and April 30, 2004, in connection with the above-identified application.

The examiner has rejected claims 51-53 and 55-64 under 35 U.S.C. § 103(a) as being unpatentable over Edelman in view of Rocklage. In addition the examiner has rejected claim 54 under 35 U.S.C. § 103(a) as being unpatentable over the same two references and further in view of Goldenberg. In rejecting the claims the examiner acknowledges that Edelman teaches the use of Gd-DTPA metal complex as the contrast agent and does not disclose the manganese complex which applicant selects as the only contrast agent utilized in the invention. The examiner turns to the teaching of Rocklage for the use of the manganese complex as the contrast agent. The examiner relies on Goldenberg in rejecting claim 54 for Goldenberg's teaching concerning the use of inversion-recovery spin-echo MRI as the spin echo MRI procedure.

The examiner has also rejected claims 51-53, 55-58 and 63-74 under 35 U.S.C. § 103(a) as being unpatentable over Edelman in view of Ericcson. In this rejection the examiner also relies on the secondary reference (Ericcson) to support the examiner's

conclusion that it would be obvious to use the manganese contrast agent of Ericcson instead of the Gd of Edelman to arrive at applicant's invention. In this regard the examiner states on page 5 of the last office action that "Ericcson teaches that Mn is an equivalent metal to Gd (as disclosed by Edelman)".

It was noted during the interview on January 20, 2004, that evidence with respect to the superiority of manganese compared to Gd as the contrast agent may be used to overcome the above-discussed rejections which rely upon the obviousness of substituting Mn for the Gd used by the primary reference (Edelman). In this regard it was noted in the paragraph bridging pages 11-12 of the amendment dated March 17, 2004, that the superiority of manganese based contrast agents over Gd-based agents in detecting myocardial ischemia have been verified in a number of scientific journal articles published after the filing date of the present application and that applicant can supply the examiner with copies of these references if necessary. Accordingly, applicant submits herewith two publications, both of which were published as articles in the scientific journal Radiology. The first is Flacke et al., Radiology 2003, 226, 731-738 and the second is Krombach et al., Radiology 2004, 230, 183-190. Applicant submits that these two publications support applicant's assertion that manganese-based agents are superior to Gd-based agents.

Flacke et al. is specifically concerned with comparing Gd-based agents and manganese-based contrast materials in detecting myocardial ischemia. The research reported in this article directly compares the two types of agents and concludes that manganese-based agents are highly specific and less sensitive to timing for infarct size determination than their Gd counter-parts (see conclusion, page 731). Furthermore, it is concluded on page 737, right column, second paragraph, that Mn-based agents may offer additional benefits (i.e., over Gd-based complexes) since they specifically enhance (for imaging purposes) viable myocardial, and the longer washout rate provides a greater window for imaging myocardial infarcts.

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Krombach et al. relates to research carried out to determine whether stunned myocardium can be delineated using MR imaging and manganese ions. The article reports that stunned myocardium was delineated with  $MnCl_2$ -enhanced MR imaging as a hypoenhanced zone (see conclusion, page 183). In contrast, the article highlights at page 188, right column, that Gd based agents have been shown to be ineffective for distinguishing stunned myocardium from normal myocardium. It is therefore clear from this publication that Mn-based agents have uses in MR imaging for which Gd-based agents cannot be used.

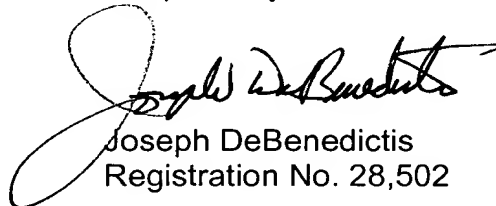
In view of the above, applicant submits that the above-discussed publications demonstrate the superiority of manganese based contrast agents over Gd-based agents which is clearly surprising in view of the examiner's observation concerning Edelman's teaching that Mn is an equivalent metal to Gd.

Date: May 18, 2004

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Respectfully submitted,



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